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FACSIMILE COVER SHEET

Examiner: P. Gambel **Group:** 1644

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From: Helen Lee

Subject: **Paper:** Declaration of Sander J.H. van Deventer, M.D., Ph.D. and Daan W. Hommes, M.D. Under 37 C.F.R. § 1.132 with Certificate of Facsimile Transmission and Transmittal letter with Certificate of Facsimile Transmission

Docket No.: 2891.1001-018 (KIR92-01A4)

Applicants: Marc Feldmann and Ravinder N. Maini

Serial No.: 08/690,775

Filing Date: August 1, 1996

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Comments:

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October 11, 2000

PATENT APPLICATION
Docket No.: 2891.1001-018 (KIR92-01A4)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Marc Feldmann and Ravinder N. Maini

Application No.: 08/690,775 Group Art Unit: 1644

Filed: August 1, 1996 Examiner: P. Gambel

For: ANTI-TNF ANTIBODIES AND METHOTREXATE IN THE TREATMENT OF AUTOIMMUNE DISEASE

CERTIFICATE OF FACSIMILE TRANSMISSION
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TRANSMITTAL OF DECLARATION OF SANDER J.H. VAN DEVENTER, M.D., PH.D. AND DAAN W. HOMMES, M.D. UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please find enclosed herewith an executed Declaration of Sander J.H. van Deventer, M.D., Ph.D. and Daan W. Hommes, M.D. under 37 C.F.R. § 1.132 for filing in the above-referenced patent application.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Helen Lee
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October 3, 2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Marc Feldmann and Ravinder N. Maini

Application No.: 08/690,775 Group Art Unit: 1644

Filed: August 1, 1996 Examiner: P. Gambel

For: ANTI-TNF ANTIBODIES AND METHOTREXATE IN THE TREATMENT OF AUTOIMMUNE DISEASE

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DECLARATION OF SANDER J.H. VAN DEVENTER, M.D., PH.D. AND DAAN W. HOMMES, M.D. UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

We, Sander J.H. van Deventer, M.D., Ph.D. and Daan W. Hommes, M.D., declare and state that:

1. We are physicians in the Department of Experimental Internal Medicine and the Department of Gastroenterology and Hepatology, Academic Medical Center, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands.

2. Twelve (12) patients with a history of steroid refractory Crohn's disease have been treated by Dr. Hommes under the supervision of Dr. van Deventer with a combination of methotrexate and anti-TNFα antibody. As described in the following section, 10 patients showed a clinical response. It is too soon to evaluate the clinical response in the remaining 2 patients.

3. The following is a description and discussion of the work carried out and of the results which demonstrate that a clinical response is obtained in patients with a history of steroid refractory Crohn's disease when treated with a combination of methotrexate and anti-TNFα antibody.

Twelve (12) patients with a history of steroid refractory Crohn's disease were treated with a combination of methotrexate (MTX) and the anti-TNFα antibody infliximab (also known as cA2 and REMICADE®). The clinical characteristics of the patients are provided in Table 1.

TABLE 1 Clinical Characteristics of Patients

Patient Number	Age (years)	Sex	History of Disease (years)	Disease Site	Fistulae	Surgery
1	35	F	17	colon	yes	colectomy
2	36	M	8	colon	no	no
3	29	F	10	small bowel	no	colectomy
4	25	F	9	small bowel	yes	IC-resection
5	22	M	>5	colon	yes	no
6	58	M	>10	colon	no	colectomy
7	27	F	6	colon	yes	colectomy
8	31	M	9	colon	yes	no
9	33	F	14	small bowel & colon	no	ileo-colectomy
10	36	M	3	colon	no	no
11	28	F	18	colon	yes	partial colectomy
12	30	F	4	colon	no	no

The treatment regimen for each patient is provided in Table 2. Methotrexate, at a dose of 25 mg/week or 15 mg/week, was administered subcutaneously (s.c.) at one week intervals for the duration indicated in Table 2. Infliximab was generally administered intravenously (i.v.) in infusions of 5 mg/kg. The number of infliximab infusions administered to each patient is indicated in Table 2. Infusions were administered generally at about 8 week intervals.

TABLE 2 Treatment Regimen

Patient Number	Duration MTX (months)	Dosage of MTX (mg/week)	Number of Infliximab Infusions
1	4	25	3
2	27	25	3
3	1	25	2
4	2	25	1
5	19	25	3
6	2	25	2
7	28	25	2 x 3
8	2	25	1
9	9	15	1
10	4	25	3
11	26	25	2
12	21	25	4

For example, patient 1 was administered methotrexate weekly at a dose of 25 mg/week s.c. for 4 months and infliximab at a dose of 5 mg/kg per infusion for 3 infusions, with each infusion administered at about 8 week intervals.

The clinical response observed for each patient after treatment with a combination of methotrexate and infliximab is provided in Table 3. Since disease activity index scores have not been determined, solid markers for disease reduction and/or remission are not available.

TABLE 3 Clinical Response of Treated Patients

Patient Number	Response
1	fistulae healing
2	clinical response only with combined MTX/infliximab; no remission
3	clinical response; no remission
4	not yet known
5	short response; MTX exchanged for azathioprine
6	clinical response only with combined MTX/inflixmab
7	initial response; no response after last 3 infliximab infusions
8	not yet known
9	remission
10	clinical response
11	remission and complete fistulae healing
12	short-lasting clinical response

Ten (10) patients showed clinical response although in 3 patients (patients 5, 7 and 12), the response was only short-lasting. Importantly, infliximab treatment alone did not induce a response in 2 patients (patients 2 and 6). However, when methotrexate was administered concurrently with infliximab, these 2 patients showed remarkable improvement.

The clinical response for patients 4 and 8 are not yet known.

4. We declare that all statements made in this Declaration of our own knowledge are true and that all statements made on information and belief are believed to be true. Moreover, these statements were made with the knowledge that willful false statements and the like made by us are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United

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States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Sander J.H. van Deventer — Date 8/10/00

Daan W. Hommes, M.D. — Date 8/10/00